Health Technology Assessment on Clinical Oncology: Diagnostic and Treatment.

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Disclosures

Conflicts of interest relevant to this presentation

- **The “Fundación Manuel Quintela” of the University Hospital receives donations for the Service of Clinical Oncology, including donations from the Pharmaceutical Industry.**

- **President (A) of the National Resources Fund (since March 2015)**

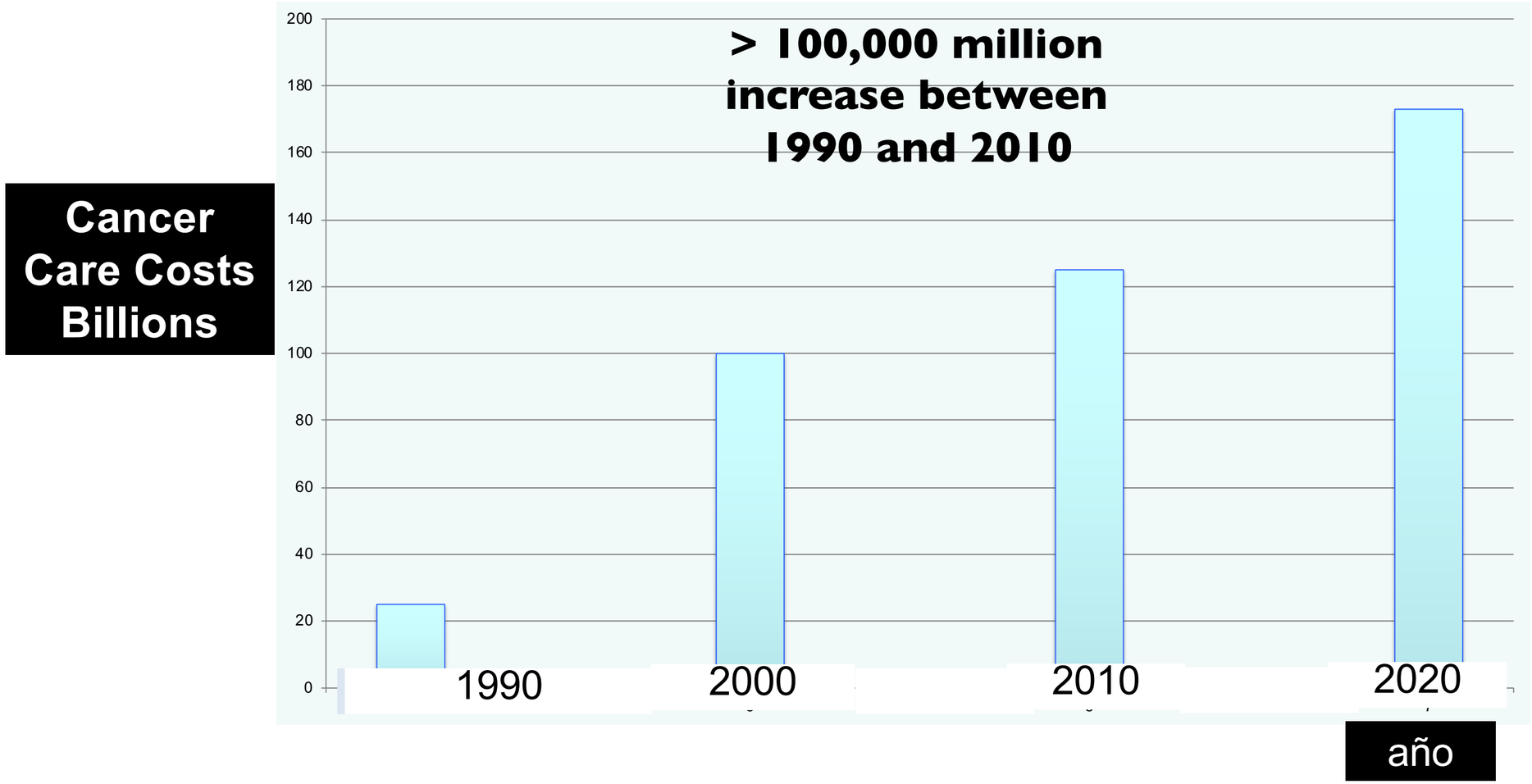
Cancer in the world: one of the main health challenges

- **Second leading cause of death worldwide**
  - **About 1 in 6 deaths**
  - **1 in 3 deaths due to Noncommunicable Diseases**
  - **70% in low- and middle-income countries**
  - **14% in the Americas**

- **Important and progressive increase of:**
  - **Incidence** (due to increased of life expectancy and lifestyle)
  - **Cancer care costs**

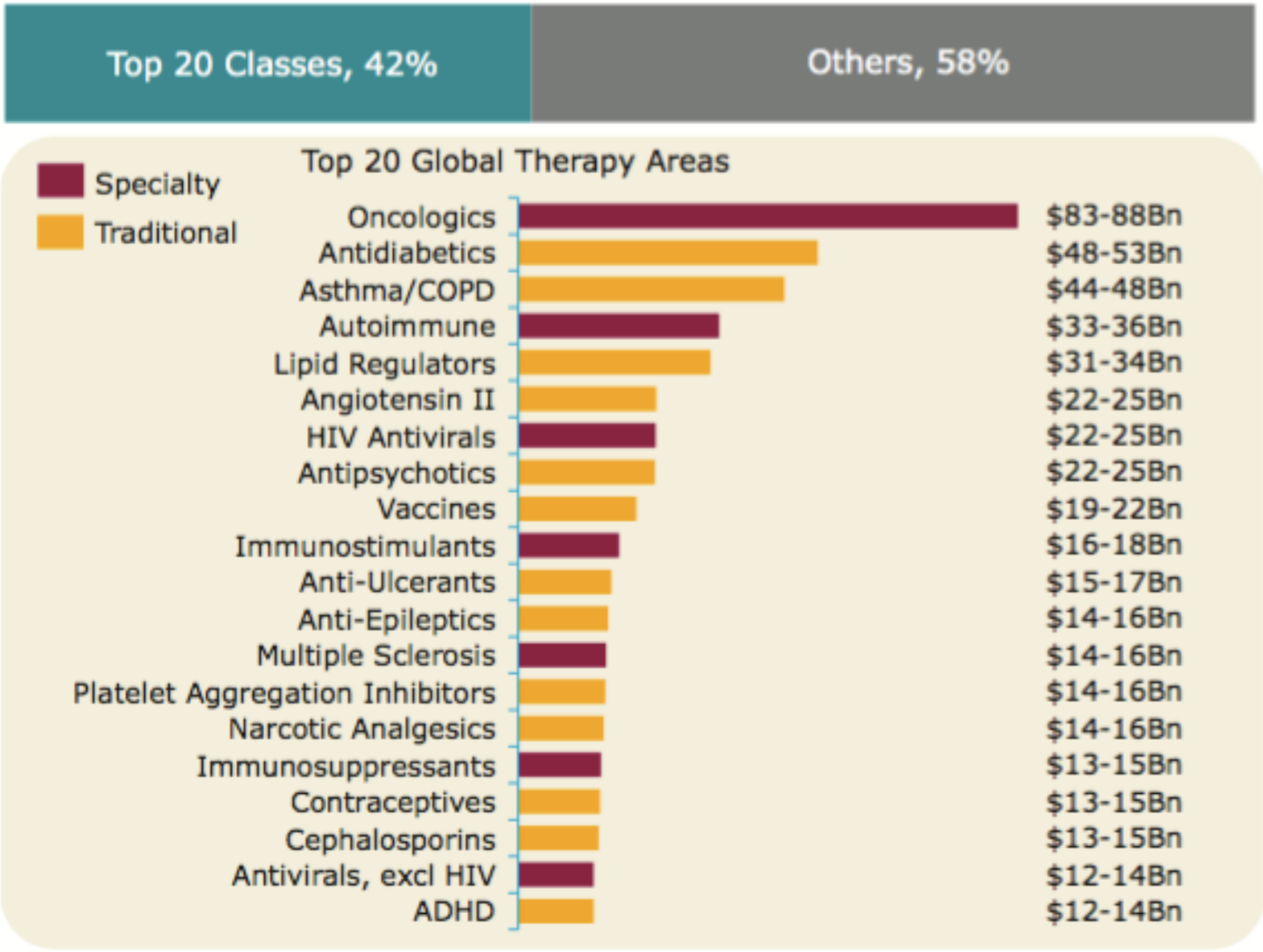
WHO 2019 https://www.who.int/es/news-room/fact-sheets/detail/cancer

Projections of the Cancer Care Costs in the US

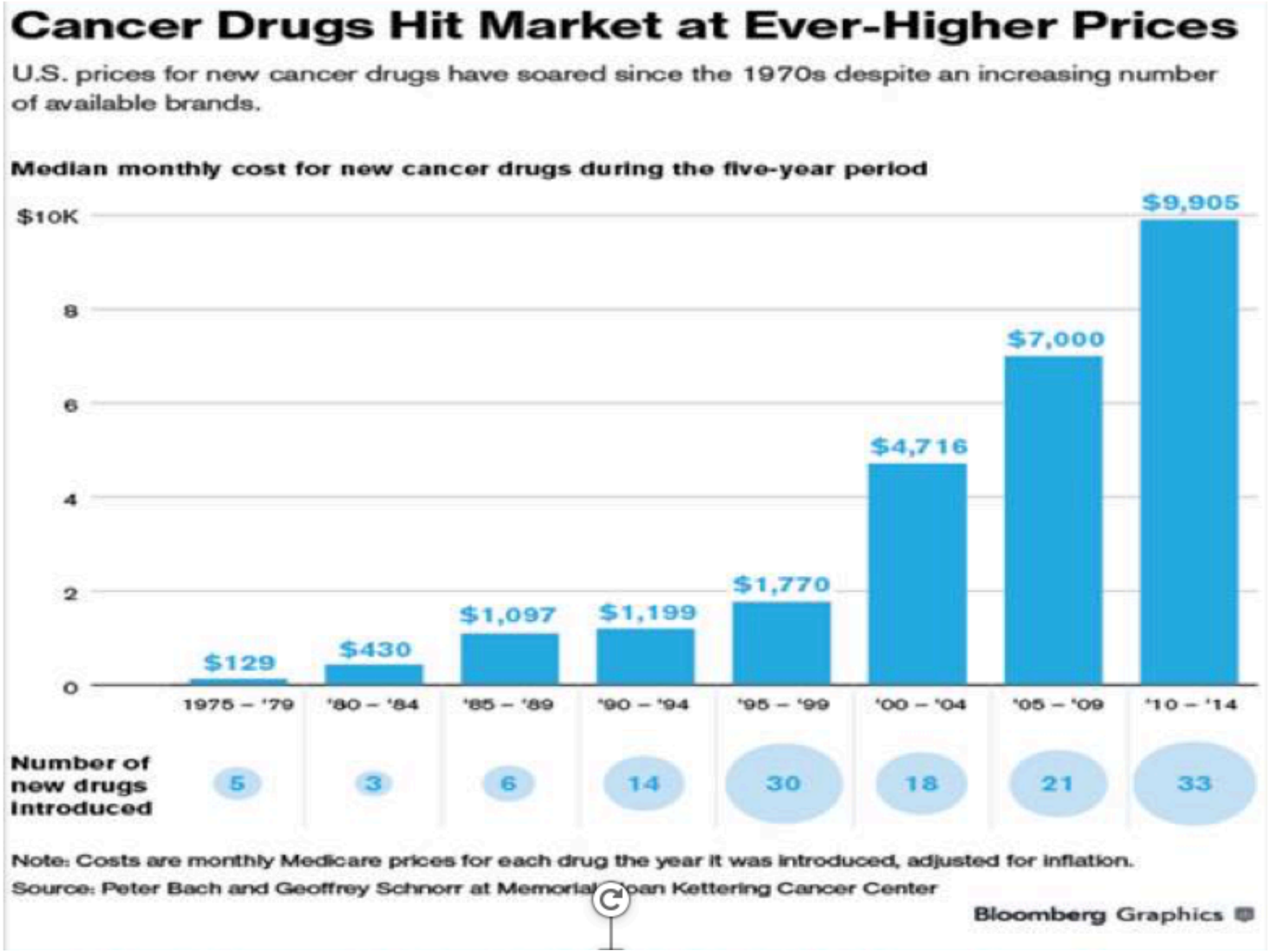


Mariotto AB, et al. J Natl Cancer Inst 2011, 19;103(2):117-28

Expenditure on medicines: cancer ranks 1st



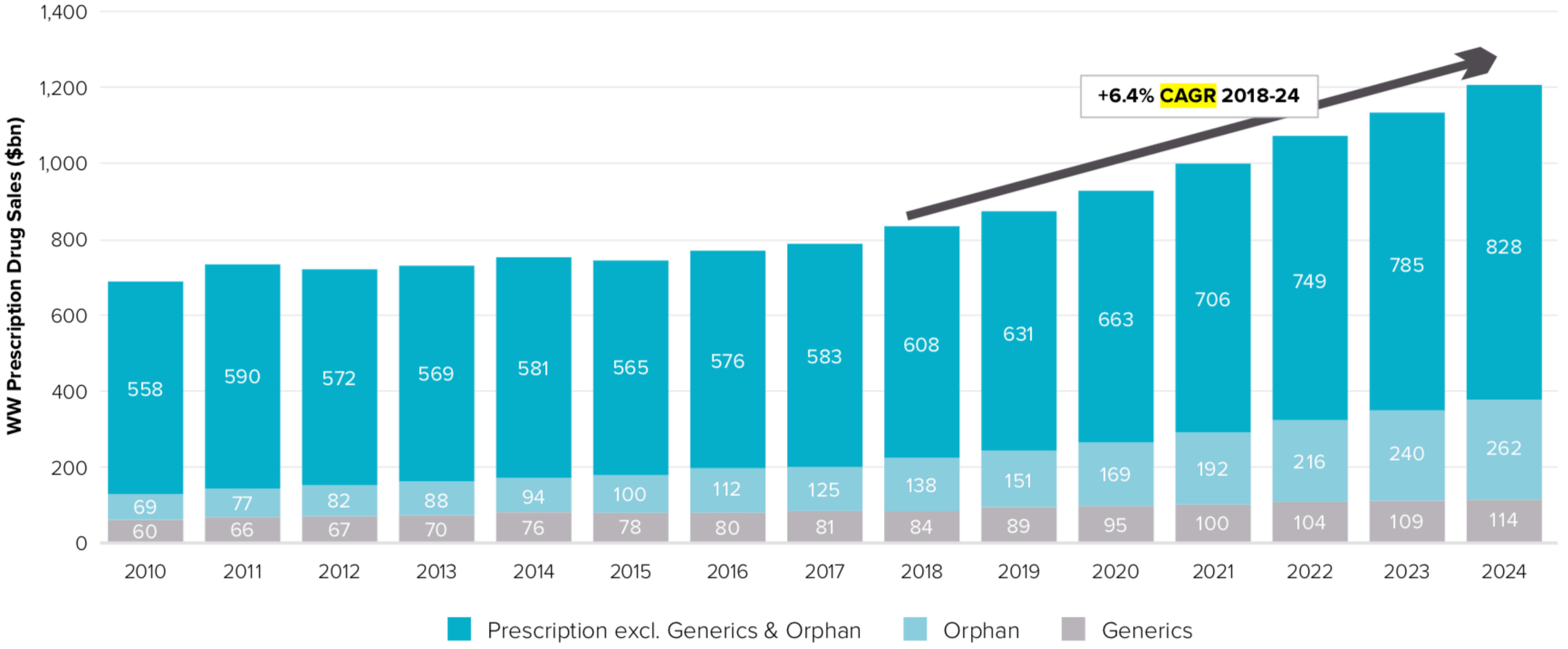
Source: IMS Institute for Healthcare Informatics, May 2012



Robert Langreth 25 de noviembre de 2014. Bloomberg News

Worldwide Total Prescription Drug Sales (2010-2024)

Source: Evaluate, May 2018



Is there a correlation between effectiveness of the new medicines and the price?

Example: **Advanced Melanoma Treatment**

Until 2011, no treatment was shown to prolong survival

Systemic Treatment of Advanced Melanoma

Main Advances: Summary

	OR %	SV (Md)	1 year SV (%)
Dacarbacina	10-25	7-9	30
Vemurafenib	48	13-14 m	55-65
Dabrafenib + Trametinib	64	18.3 m	72
Ipilimumab	11	10-11m	45-60
Nivolumab	40		70
Pembrolizumab	45		75-80
Nivo + Ipi	50-60	-	-

prices?

Estimated Treatment Price

For a patient of 80 kg and during median progression free survival

Treatment	Price (U$S)
Dacarbazine (*) x 3 months	**230**
Nivolumab (**) x 6.9 months	**103.220**
Ipilimumab (**) x 2.9 months	**158.252**
Nivolumab + Ipilimumab (**) x 11.9 months	**295.566**
Vemurafenib x 5 months	**36.200**

(*) Estimate based on prices of UCA 2015

(**) Estimate based en prices includes in ASCO 2015 presentation of Prof. Leonard Saltz

Vemurafenib vs Dacarbazine

EFFECT

(1 year survival)

X 2

PRICE

X 157

Nivolumab vs Dacarbazine

EFFECTO

(1 year survival)

X 2.3

PRICE

X 448

Trastuzumab + Docetaxel vs Pertuzumab + Trastuzumab + Docetaxel

as first line therapy for HER2 positive Advanced Breast Cancer

	Median SV months
Trastuzumab-Docetaxel (PFS 12.4)	40.8
Pertuzumab-Trastuzumab- Docetaxel (PFS 18.7)	**56.5**

Estimated Treatment Price

For a patient of 70 kg and 1.7 m2 treated during the median progression free survival

	Price (U$S)
Trastuzumab (*)-Docetaxel (**) (12.4)	14.200
Pertuzumab +Trastuzumab +Docetaxel (18.7)	97.000

(*) Estimated based on data of the FNR
(**) Estimated bases on prices of UCA 2015

Pertuzumab +T+D ***vs*** *T+D*

EFFECT

(Median SV)

X 1.4

PRICE

X 6.8

HIGH COST/PRICE

IS THE MAIN BARRIER TO ACCESS

ACCESS AND RATIONAL USE OF STRATEGIC AND HIGH-COST MEDICINES AND OTHER HEALTH TECHNOLOGIES

PAHO-WHO 2016

Equitable access to medicines and other health technologies is **a requisite for universal access to health and universal health coverage**, and it is a **global priority** which should be considered within the context of the **principle that recognizes the enjoyment of the highest attainable standard of health for all.**

The availability, accessibility, acceptability, and affordability of these medical products and their rational use can be facilitated through the **adoption of comprehensive policies, legal and regulatory frameworks, and interventions.**

However, the **escalating costs of providing access to high-cost medical products**, poses a particular **challenge** for the **sustainability of health systems**.

https://www.paho.org/hq/dmdocuments/2016/CD55-10-e.pdf

Incorporation of Diagnostic Studies and Treatments to Universal Health Coverage

Countries that have **health systems with universal coverage** and **equity,** systematically perform **efficacy and safety assessments** and **economic evaluations** for decision-making about the incorporation of new technologies.

This process is necessary because:
- Not all innovation is an advance.
- Not all innovation improves health.
- Lack of correlation between the allocation of economic resources to health technologies and the obtaining of favorable results in health indicators (morbidity, mortality, healthy years of life gained).

Process of Incorporation of Healh Technologies

- **Nomination of technologies** to be assessed (diagnostic, therapies)
- **HTA**: applying methodological guides with HTA reports publicly available.
- **Prioritization of technologies to be incorporated** (with the participation of the different stakeholders, including academy, patients movements, policy makers and politicians)
- **Recommendation**
- **Decision making based** on HTA, priorization and budget impact

Why is it necessary to establish a prioritization of new technologies with a net benefit?

Stages in the prioritization process

1.- Verify safety, efficacy and quality (necessary for marketing approval).

2.- Determine the convenience of evaluating the HT: selection of evaluation candidates.

3.- Evaluation of efficiency, effectiveness and budgetary impact: to determine the **VALUE** (HT evaluation in order to establish recommendations for inclusion).

4.- Process of deliberation (interested parties are heard, existing evaluations are taken into account) for making the decision: it is resolved whether or not technology should be prioritized and financed with public resources.

5.- Process monitoring and evaluation of the incorporated HT

What's the **value** of medicines in public health?

HOW TO DEFINE THE CLINICAL VALUE OF THE NEW THERAPIES

- The value of any new treatment is determined by the balance between the magnitude of its clinical benefit and its cost.

$$\textbf{Clinical Value} \approx \frac{\textbf{clinical benefit}}{\textbf{toxicity + cost}}$$

J Clin Oncol. 2016;34(24):2925-34
Annals of Oncology 2015;26: 1547–1573,

- In an era of **rapid expansion of new therapies** and other **high-priced technologies**, it is increasingly important to consider **CLINICAL VALUE**

CLINICAL BENEFIT

- Main therapeutic objectives:
- - prolong **patient survival**
- - Improve **Quality of Life**

- **Progression free survival**

- Not always predict longer Overal Survival or longer survival free of symptoms

- Its value depends on the balance between toxicity associated with treatment and reduction or delay of symptoms due to relapse

What the regulatory agencies approvals?

- **More than 50% of the drugs approved by FDA/EMA have never showed a gain in survival in the clinical trials of approval.**

- **And the other thing is that the average gain of overall survival and progression free survival is less than three months when we consider all the medicines together.**

BMJ; 2017; 359:J4530
JAMA Int Med 2015;175:1992-4

REPORT Pricing of cancer medicines and its impacts. World Health Organization 2018
https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf

NEVERTHELESS……..

FDA: **according to the code of Federal Regulations, the criteria for drug approval require substantial evidence of clinical benefit (higher SVG and / or better quality of life) from adequate and well-controlled studies.**

Code of Federal Regulations, Part 314.126. U.S. Government Publishing Office. http://www.ecfr.gov. Accessed October 20, 2017.

But, in the last 40 years there has been a relaxation of the criteria to approve anticancer therapies, with numerous accelerated approvals

MAGNITUDE OF CLINICAL BENEFIT

- **Evidence of clinical benefit:**
  - It comes from clinical trials, especially phase III randomized trials

Magnitude of clinical benefit: how to rate it?

- To date there is no standard tool

- ASCO and ESMO have developed tools for their evaluation

ASCO AND ESMO scales to measure CLINICAL VALUE

- **Prioritize the prolongation of the SV and the improvement of the quality of life**
- **Two versions: for advanced disease and for adjuvance**

Journal of Clinical Oncology, 34, (24): 2925-2934.,2016
Annals of Oncology 26: 1547–1573, 2015

https://www.esmo.org/Guidelines/ESMO-MCBS/Scale-Evaluation-Forms-v1.0-v1.1/Scale-Evaluation-Forms-v1.0

ESMO

A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherny[1]*, R. Sullivan[2], U. Dafni[3], J. M. Kerst[4], A. Sobrero[5], C. Zielinski[6], E. G. E. de Vries[7] & M. J. Piccart[8,9]

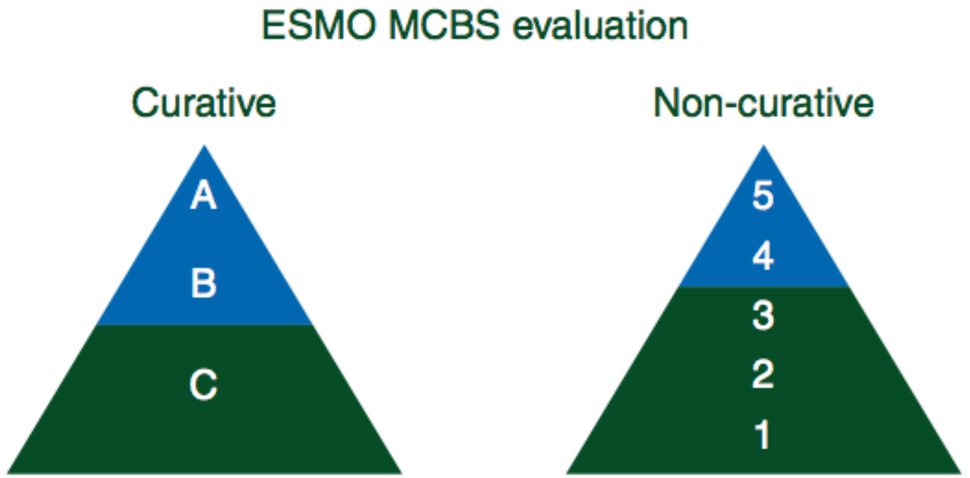


Figure 3. Visualisation of ESMO-MCB scores for curative and non-curative setting. A & B and 5 and 4 represent the grades with substantial improvement.

Annals of Oncology 26: 1547–1573, 2015

Scales to estimate CLINICAL BENEFIT

ASCO Value Framework

Scores are calculated for:

Clinical Benefit
Toxicity
Extra bonus
(valor agregado)

The scores are combined into a score called

Net Benefit

Cost

Journal of Clinical Oncology, 34, (24): 2925-2934.,2016

Clinical significance vs. statistical significance

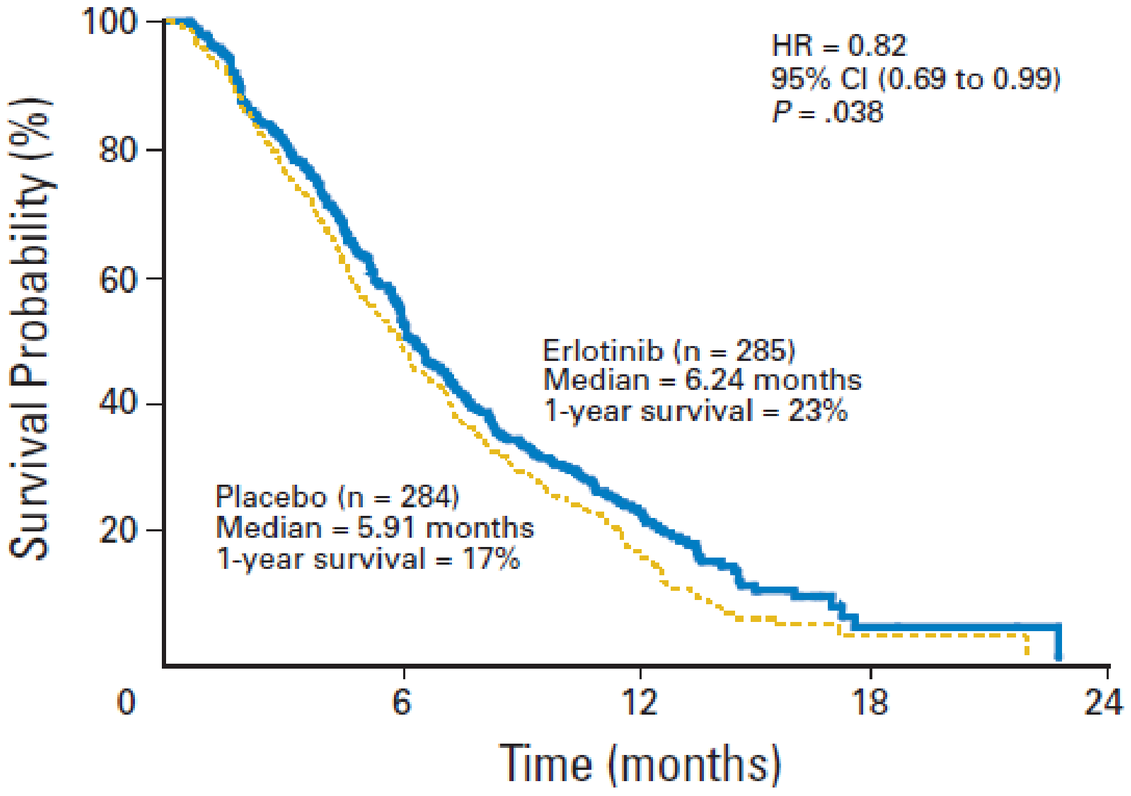
Significant Clinical Benefit

- **Several studies have shown a statistically significant benefit. but CLINICALLY not significant**

- **FDA / EMA have approved drugs based on any statistically significant difference**

Erlotinib Plus Gemcitabine Compared With Gemcitabine Alone in Patients With Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group

Malcolm J. Moore, David Goldstein, John Hamm, Arie Figer, Joel R. Hecht, Steven Gallinger, Heather J. Au, Pawel Murawa, David Walde, Robert A. Wolff, Daniel Campos, Robert Lim, Keyue Ding, Gary Clark, Theodora Voskoglou-Nomikos, Mieke Ptasynski, and Wendy Parulekar



Sobrevida mediana:
6.24 vs 5.91 meses

Pese a esta diferencia trivial en la Sobrevida, *la misma fue estadísticamente significativa ..*

y

Erlotinib + Gemcitabina *fue aprobado por la FDA para el tratamiento del cáncer de páncreas*

Costo incremental por año de vida ganado:
U$S 430.000

Miksad R et al. JCO 2007;25(28): 4506-4507

WHO recommends in terms of value-based policy for the prioritization of medicines

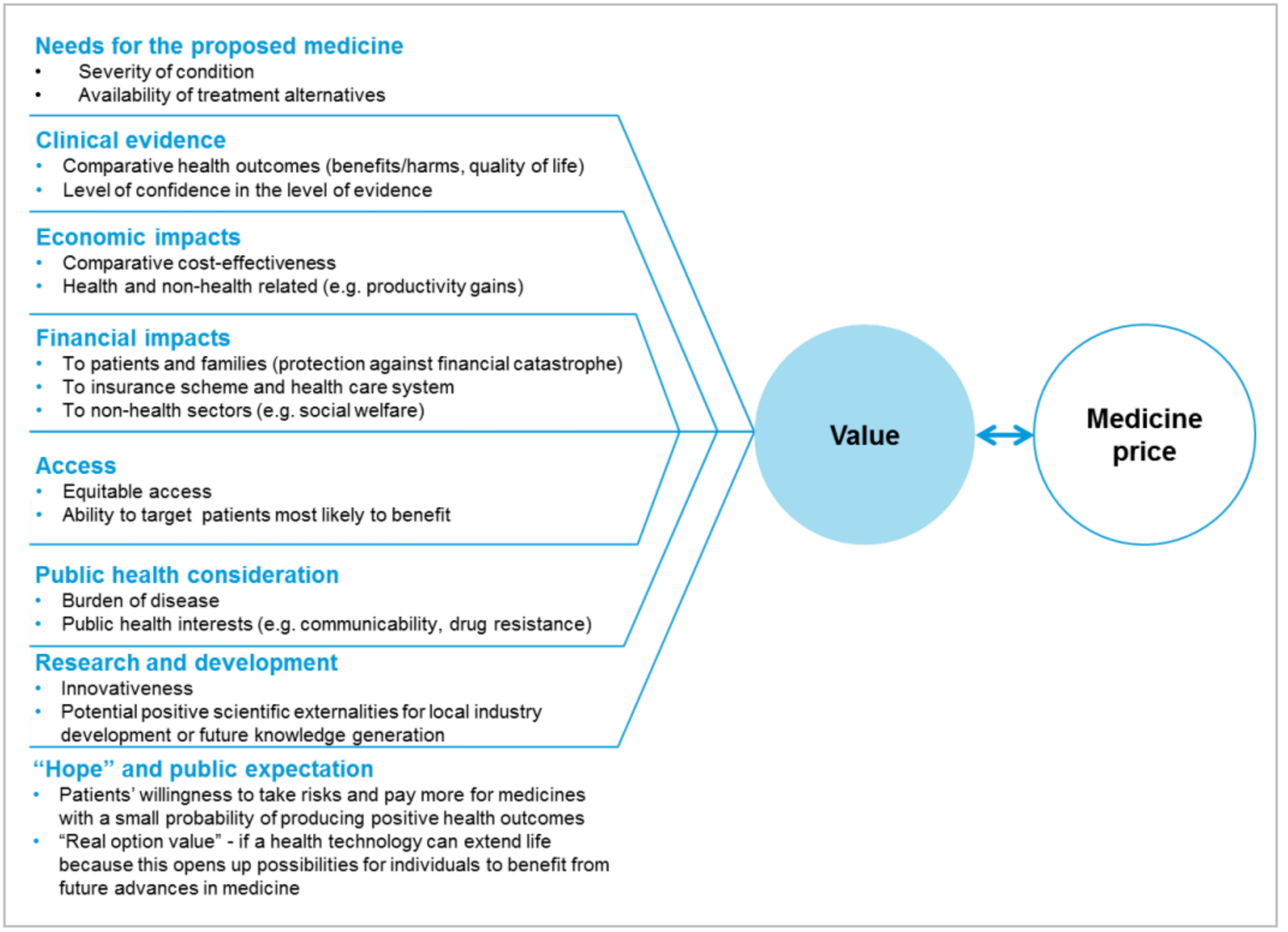
1) to select the essential medicines for this country according to the **cancer epidemiology and to** the **health system capacity**, because some of these medicines **closely related to companion diagnostic.** Ej: Trastuzumab

2) to promote **collaboration, to foster collaboration among countries, to share the information on health technology assessment**

3) to **correct the misperception of inferior quality of generics and biosimilar.**
(Substituing the branded monoclonal antibody, ii is possible to save up to a lot of billion euro during the next 1-2 years)

REPORT Pricing of cancer medicines and its impacts. World Health Organization 2018
https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf

Fig. 3.8: Dimensions that may be considered for determining the value of medicines



Source: (*110,111,156,161,162*)

Value –based prioritization

- **Value-based prioritization is definitely a priority for global oncology and is relevant for all cancer interventions**
- **Value can be estimated.**
- **Non-value-based prioritization results in a worst outcome for patients.**
- **HTA is the setting to make the value-based decision.**

Dario Trapani, ASCO Annual Meeting 2019

Conclusions

- **Health care costs have increased significantly and are not sustainably**

- **The increase in the price of new drugs is NOT proportional to the increase in clinical benefit and is NOT explained by investment in research and development**

- **Although several of the new therapies can significantly prolong survival, their cost determines that they are not cost-effective, even for the richest countries**

It is ESSENTIAL:

- To make **value-based decisions** in the setting of **HTA** and to make **value–based prioritization.**

- Promote the **participation of the different stakeholders** in the **value bsed prioritization process**

- **Improve actions aimed at health promotion and prevention**

Gracias!!

HIGH COST or HIGH PRICE?

What should be the main criteria for prioritizing new diagnostic or therapeutic procedures:

Cost-effectiveness?

Effectiveness?

The Magnitude of Clinical Benefit?

The budget impact?

Others?

judicialization of the right to health:
is mostly used to access high-price treatments

Why not for other treatments like **radiotherapy**
for which there is often no access?